CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-011

ADMINISTRATIVE DOCUMENTS

13.0 Patent Information

Reference is made to the subject NDA for immediate release oxycodone hydrochloride for the treatment of moderate to severe pain and the requirements of 505(b) of the Federal Food, Drug as Cosmetic act as amended and 21 CFR 314.50(h).

Section 355(b)(1) of the Pure Food and Drug Act requires that "The applicant shall file with the [New Drug] application the patent number and expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug."

Based on searches conducted in the Dialog Patents database and the U.S. Patent Office database system, no U.S. patent contains a claim or use which includes immediate release oxycodone hydrochloride.

Therefore, to the best of our knowledge at the time of this filing, no patent claims the drug referred to in this application or claims a use for the drug.

APPEARS THIS WAY
ON ORIGINAL

Patent Certification

In the opinion and to the best knowledge of Roxane Laboratories, Inc., there are no patents that claim the drug [single entity immediate release oxycodone hydrochloride 15 and 30 mg)] on which investigations that are relied upon in this application were conducted or that claim a use of such drug.

Gerry Perez
Senior Vice President, Technical Operations
Roxane Laboratories, Inc.

3 Feb 2000
Date

APPEARS THIS WAY
ON ORIGINAL

14.0 Patent Certification

Reference is made to the subject NDA for single entity immediate release oxycodone hydrochloride (15 and 30 mg) in the treatment of moderate to severe pain and the requirements of 505(b)(2) of the Federal Food, Drug and Cosmetic Act as amended.

Roxane Laboratories, Inc. certifies, in its opinion and to the best of its knowledge, with respect to each patent which claims the drug for which investigations were conducted or which claims a use for such drug for which Roxane Laboratories, Inc. is seeking approval under 505(b)(2) and for which information is required to be filed under paragraph (1) or subsection (c) that such patent information has not been filed.

Based on the above Patent Information and Certification, the approval of the referenced product may be made immediately effective.

APPEARS THIS WAY
ON ORIGINAL

13.0 Patent Information

Reference is made to the subject NDA for immediate release oxycodone hydrochloride for the treatment of moderate to severe pain and the requirements of 505(b) of the Federal Food, Drug as Cosmetic act as amended and 21 CFR 314.50(h).

Section 355(b)(1) of the Pure Food and Drug Act requires that "The applicant shall file with the [New Drug] application the patent number and expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug."

Based on searches conducted in the Dialog Patents database and the U.S. Patent Office database system, no U.S. patent contains a claim or use which includes immediate release oxycodone hydrochloride.

However, there are patents for combination, alternative delivery, and controlled-release drug products that include oxycodone salts:

<u>Combination Products</u>

U.S. Patent No. 5468744 (21 Nov 1995) McNeilLab, Inc.

> Synergistic composition comprised of tramadol derivative and opioid compound (i.e., oxycodone) for treating pain, diarrhea, and tussive conditions.

U.S. Patent No. 4769372 (6 Sept 1988) Rockefeller University

> Comprised of opioid analgesic – antitussive, opioid antagonist combination for the treatment of pain or cough without causing intestinal problems.

U.S. Patent No. 4569937 (11 Feb 1986) Du Pont de Nemours & Co.

> Comprised of synergistic analgesic combination of oxycodone and ibuprofen or acceptable salts.

U.S. Patent No. 4599342 (8 July 1986) Proctor & Gamble Co.

> Comprosed of synergistic analgesic composition containing capsaicinoid and opioid compounds (i.e., oxycodone).

U.S. Patent No. 4576951 (18 Mar 1986) Rotta Research Lab Spa

> Comprised of proglumide and opioid (i.e., oxycodone) combination for the treatment of pain and potentiating narcotics.

U.S. Patent No. 4464376 (7 Aug 1984) Richardson Vicks, Inc.

> Comprised of analgesic (i.e., oxycodone) and anti-inflammatory composition.

U.S. Patent No. 4610989 (8 Sept 1986) Hoffman-LaRoche AG

Comprised of a synergistic analgesic composition containing an opiate alkaloid (i.e., oxycodone) and 6-chloro-alpha-methyl-carbazole-2-acetic acid.

U.S. Patent No. 4366159 (28 Dec 1982) Magruder M R

Comprised of an analgesic composition containing morphine etc. (i.e., oxycodone) with nalbuphine to reduce respiratory depression.

Alternate Delivery Products

U.S. Patent No. 5451408 (19 Sept 1995) Liposome Pain Management, Ltd.

Composition for pulmonary administration of liposome-encapsulated opioid analgesic (i.e., oxycodone)

U.S. Patent No. 6629011 (13 May 1997) Danbiosystems, UK, Ltd.

Composition (polar metabolites of opioid analgesics, i.e., oxycodone, and an absorption-promoting agent) for the nasal administration of pain relief.

U.S. Patent No. 4879279 (11 Nov 1989) Warner Lambert Co.

Composition of transdermal delivery of natural or synthetic opioid analgesics (i.e., oxycodone) to the circulatory system.

U.S. Patent No. 5317022 (31 May 1994) and 5457110 (10 Oct 1995) Alkaloida Chemical Co.

Preparation containing codeinone, oxycodone, or dihydrocodeinone derivatives for the selective blockade of opioid binding sites in the brain responsible for respiratory depression.

U.S. Patent No. 4626539 (2 Dec 1986) Du Pont de Nemours & Co.

Composition for the transdermal delivery of opioids (i.e., oxycodone).

Controlled-Release Products

U.S. Patent No.5656295 (12 August 1997) Euroceltique, S.A.

Controlled-release formulation of oxycodone hydrochloride for oral administration.

U.S. Patent No. 5508042 (16 Apr 1996) Euroceltique, S.A.

Reduction in range of total daily dose to control pain with controlled-release oxycodone hydrochloride for oral administration.

U.S. Patent No. 5500227 (19 May 1996) Euroceltique, S.A.

Sustained-release oxycodone hydrochloride tablet for oral administration

U.S. Patent No. 5286493 (15 Feb 1994) Euroceltique, S.A.

Preparation of stable controlled-release formulations

U.S. Patent No. 5266331 (30 Nov 1993) Euroceltique, S.A.

Controlled-release oxycodone formulation for oral administration

U.S. Patent No. 5549912 (27 Aug 1996) Euroceltique, S.A.

Controlled-release oxycodone formulation for oral administration

U.S. Patent No. 5273760 (28 Dec 1993) Euroceltique, S.A.

Stabilized controlled-release substrate

U.S. Patent No. 4861598 (29 Aug 1989) Euroceltique, S.A.

Controlled-release oral pharmaceutical composition

U.S. Patent No. 4970075 (13 Nov 1990)) Euroceltique, S.A.

Extended patent for release of therapeutically active agents (i.e., oxycodone) from controlled-release bases

U.S. Patent No. 5478577 (26 Dec 1995) Euroceltique, S.A.

Method of treatment of pain by administering a 24h oral opioid (i.e., oxycodone) formulation exhibiting rapid rate of initial rise of plasma drug level

The patents cited above do not list single entity immediate realease oxycodone hydrochloride for the treatment of moderate to severe pain. Therefore, to the best of our knowledge at the time of this filing, no patent claims the drug referred to in this application or claims a use for the drug.

Based on the above information and Certification, the approval of the referenced product may be made immediately effective.

APPEARS THIS WAY
ON ORIGINAL

14.0 Patent Certification

Reference is made to the subject NDA for single entity immediate release oxycodone hydrochloride (15 and 30 mg) in the treatment of moderate to severe pain and the requirements of 505(b)(2)(a) of the Federal Food, Drug and Cosmetic Act as amended.

Roxane Laboratories, Inc.offers the following Patent Certification with respect to the drug which is the subject of this submission.

Based on searches conducted in the Dialog Patents database and the U.S. Patent Office database system, no U.S. patent contains a claim which includes single entity immediate release oxycodone hydrochloride (15 and 30 mg). Therefore, to the best of our knowledge at the time of this filing, no patent exists for single entity immediate release oxycodone hydrochloride (15 and 30 mg).

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Roxane Laboratories, Inc.
Columbus, Ohio

NDA 21-011
ROXICODONE™ Tablets
(Oxycodone HCl Tablets, USP)

Patent Certification

In the opinion and to the best knowledge of Roxane Laboratories, Inc., there are no patents that claim the drug [single entity immediate release oxycodone hydrochloride 15 and 30 mg tablets)] on which investigations that are relied upon in this application were conducted or that claim a use of such drug.

Kirk V. Shepard, M.D.
Senior Vice President
Marketing, Medical and Regulatory Affairs, and
Product Development
Roxane Laboratories, Inc.

9.11.03
Date

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ON ORIGINAL

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PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

\/PLA/PMA # 21-011 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-170 Trade and generic names/dosage form: Roxicodone 15 and 30 mg (oxycodone hydrochloride) tablets Action: AE
Applicant: Roxane Laboratories Inc. Therapeutic Class 3S

Indication(s) previously approved:
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X
Proposed indication in this application Management of moderate to severe pain where the use of an opioid analgesic is appropriate

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? X Yes (Continue with questions) _ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) X Children (2-12yrs) X Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
- ___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- ___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- X c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - X (4) If nc protocol has been submitted, attach memo describing status of discussions.
- ___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

X 5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**
- X a. Pediatric studies are needed.
- ___ b. Pediatric studies may not be needed but a pediatric supplement is needed.

___ 6. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? X Yes ___No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ MD, Division Director HFD-170 9/15/99

Signature of Preparer and Title Date

Orig NDA/PLA/PMA # 21-011
HFD-170/Div File
NDA/PLA Action Package
HFD-006/ KRoberts

(revised 9/15/97)

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021011	**Trade Name:**	ROXICODONE (OXYCODONE HCL) TBS 15/30 MG
Supplement Number:	000	**Generic Name:**	OXYCODONE HCL
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	AE	**COMIS Indication:**	MANAGEMENT OF MODERATE TO SEVERE PAIN WHERE USE OF AN OPIOID ANALGESIC IS APPROPRIATE.
Action Date:	9/23/99		

Indication # 1 Management of moderate to severe pain where the use of an opioid analgesic is apprpriate
Label Adequacy: Inadequate for ALL pediatric age groups
Forumulation Needed: Other
Comments (if any): new formulation might be needed

Lower Range	Upper Range	Status	Date
0 months	1 months	Deferred	9/2/02
1 months	2 years	Deferred	9/2/02
2 years	12 years	Deferred	9/2/02
12 years	16 years	Deferred	9/2/02

This page was last edited on 8/31/00

[/S/] 8/31/00 –

Signature - Date

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Exclusivity Checklist

NDA: 21-011				
Trade Name: Roxicodone				
Generic Name: oxycodone hydrochloride				
Applicant Name: Roxane Laboratories				
Division: Anesthetic, Critical Care and Addiction Drug Products HFD-170				
Project Manager: Judit Milstein				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes		No	X
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation: Study # XIR0299 (315-23), submitted with this application, is a pK study to assess the bioavailability of oxycodone following a single dose of oxycodone hydrochloride 15mg immediate release tablet compared with a three-tablet dose of Percodan®. This bridging study was requested in the approvable letter dated September 23, 1999, in order to establish safety for the proposed higher doses.				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	X	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	3			
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	X
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously	Yes	X	No	

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approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product **See Orange Book , 20th Edition, Page 3-260**				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	X
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				

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a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:				
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential				

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to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1				
Investigation #2				
Investigation #3				
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?				
Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	
If yes, explain:				

/S/ 8/31/00

Judy Milstein, Regulatory Project Manager date

/S/ 8/31/00

Cynthia G. McCormick, M.D., Division Director date

CC:
Original NDA
Division File
HFD-93 Mary Ann Holovac

File: C:\N21011 roxicodone\excsumm.doc

APPEARS THIS WAY
ON ORIGINAL

16.0 Debarment Certification

A Debarment Certification as specified by the Generic Drug Enforcement Act of 1992 is provided.

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Certification of Compliance with Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Roxane Laboratories, Inc. hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there are no convictions of the applicant and affiliated persons at Roxane Laboratories, Inc. responsible for the development or submission of the application.

Gerry Perez
Senior Vice President, Technical Operations
Roxane Laboratories, Inc.

3 Feb 2000
Date

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ON ORIGINAL

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16.0 Debarment Certification

A Debarment Certification as specified by the Generic Drug Enforcement Act of 1992 is provided.

APPEARS THIS WAY
ON ORIGINAL

Roxane Laboratories, Inc.
Columbus, Ohio

NDA 21-011
ROXICODONE™ Tablets
(Oxycodone HCl Tablets, USP)

Certification of Compliance with Generic Drug Enforcement Act

In compliance with the Generic Drug Enforcement Act of 1992, Roxane Laboratories, Inc. hereby certifies that (1) we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306 (a) or (b)], in connection with this application, and (2) there are no convictions of the applicant and affiliated persons at Roxane Laboratories, Inc. responsible for the development or submission of the application.

Kirk V. Shepard, M.D.
Senior Vice President, Marketing,
Medical Affairs and Product Development
Roxane Laboratories, Inc.

9.9.98
Date

APPEARS THIS WAY
ON ORIGINAL

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15 September 1998

Sean Alan Reade
Director, Regulatory Affairs
Roxane Laboratories, Inc.
P O Box 16532
Columbus, OH 43216

Dear Mr. Reade:

[redacted] certifies that to the knowledge of the Company, it did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) of Section 306 (k) (1) of the Federal Food, Drug and Cosmetic Act, in connection with provision of professional services to Roxane Laboratories, Inc. for NDA 21-011, Oxycodone [redacted] Tablets, Study Numbers XIR 0196, XIR 0296, XIR 0396, XIR 0596, and XIR 0696.

[redacted] also certifies that to the knowledge of the Company, no employees responsible for provision of professional services to Roxane Laboratories, Inc. for the Oxycodone project under Section 306 (k) (2) of the Federal Food, Drug and Cosmetic Act have convictions described in subsections (a) and (b) occurring within the previous five years.

Sincerely,

[redacted]

cc: Master Study and Regulatory Files

APPEARS THIS WAY
ON ORIGINAL

19.0 Other (Disclosure: Financial Interests and Arrangements of Clinical Investigators)

A signed Form FDA-3455 is provided for Protocol No. 315-23, "A Pharmacokinetic Study to Assess the Bioavailability of Oxycodone Following a Single Dose of an Oxycodone Hydrochloride 15 mg Immediate Release Tablet Compared to a Three-Tablet Dose of Percodan®."

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
[redacted]	Protocol No. 315-23

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Sean Alan F.X. Reade, M.A.	Director, Drug Regulatory Affairs New Drugs and Regulatory Services
FIRM/ORGANIZATION: Roxane Laboratories, Inc.	
SIGNATURE: Sean Alan F.X. Reade	DATE: 10 February 2000

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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: August 31, 2000

TO: File, NDA 21-011

FROM: Bob A. Rappaport, M.D. [/S/]
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

THROUGH: Cynthia G. McCormick, M.D. [/S/]
Director, DACCADP

RE: Supervisory Review of NDA 21-011, Response to Approvable Letter, for Roxicodone™ (oxycodone HCl) 15 and 30 mg tablets

BACKGROUND:

NDA 21-011 was originally submitted on September 30, 1998. The application requested approval of new 15 mg and 30 mg dose strengths of the sponsor's marketed, although unapproved, 5 mg oxycodone tablets [see Division Director's Memo to File dated September 21, 1999]. The application was found to be approvable and the following deficiencies were presented to the sponsor in a letter dated September 23, 1999:

1. No data to support effectiveness were included in the NDA as comparative studies included only the subject of this application and/or the unapproved 5 mg tablets.
2. Neither waiver of the necessary studies to establish efficacy nor justification for why these studies were not needed were included in the application.
3. Clinical safety had not been adequately established at the higher doses based on the database submitted, which correlated adverse events by tablet size rather than dose.
4. The application had been filed as a 505(b)1, although it provided little to no clinically useful effectiveness data.

The letter requested that the sponsor correct those deficiencies by:

1. Performing a relative bioavailability study, bridging their product to a previously approved product.
2. Providing an adequate rationale for extension of the dosage form to the 15 and 30 mg tablets in the absence of clinical evidence of efficacy.
3. Providing sufficient evidence of safety at the higher doses either by clinical studies or by a bridging study which demonstrates relative bioavailability to a previously approved product, including retabulation of all adverse events by total daily dose for the immediate release formulation.
4. Providing the appropriate documentation and forms to designate the application as a 505(b)(2) application
5. Provide appropriate annotation and citation to the sources for all factual material referenced in labeling.

A complete response to the approvable letter was received from the sponsor on February 29, 2000.

CLINICAL PHARMACOLOGY:

This submission included the results of a bioequivalence [BE] study (XIR0299) which assessed the dose-adjusted bioavailability of oxycodone comparing immediate release oxycodone HCl 15-mg tablet with three tablets of Percodan®. Study XIR0299 was reviewed by Shinja R. Kim, Ph.D. Dr. Kim found that the results of this BE study, "...showed that [the] 90% confidence intervals around the log transformed and dose normalized ratios...excluding subjects who vomited after dose administration, for AUC_t, AUC_∞, and C_{max} were...within the BE criteria of 80-125%...[and that]...Corresponding values in all subjects...including patients who vomited post dose..." were also within the BE criteria. Dr. Kim was able to "...conclude that 15 mg oxycodone HCl immediate release tablet formulation...and 3 tablets of Percodan®...are bioequivalent with respect to oxycodone." [page 1 of the Clinical Pharmacology and Biopharmaceutics Review]

DSI

An inspection of the pivotal biopharmaceutics study was not requested. There were no irregularities in the data that would suggest due cause for an inspection and this NDA, while officially a 505b2 application for the immediate release product, is also a line extension of the 5-mg product that has been in use for decades.

PRECLINICAL TOXICOLOGY:

Also included in this submission were four preclinical Segment II reproductive toxicity studies of oxycodone hydrochloride which, although not responses to the deficiencies

cited in the approvable letter, were in response to an agreement reached between the Division and the sponsor during a meeting on December 15, 1999 and a teleconference on February 11, 2000. These studies were reviewed by BeLinda A. Hayes, Ph.D. Dr. Hayes concluded that oral administration of oxycodone was not teratogenic or embryo-fetal toxic. Also agreed upon during the above referenced meeting was the completion of a full battery of carcinogenicity studies as a Phase 4 commitment. The proposals for these studies have been submitted to the Division, and are under separate review.

CLINICAL SAFETY:

The sponsor also submitted a rationale for the development of the higher doses of oxycodone and a reassessment of the safety data, as requested in the approvable Letter. These sections of the response were reviewed by Harold Blatt, D.D.S.

Rationale for the Development of Higher Doses:

The sponsor reports that based on a review of literature, in controlled clinical trials in cancer patients, total daily doses [TDD] of oral morphine needed to control pain averaged 100 to 300 mg and at times exceeded 1000 mg. A 1:1 or 1:1.5 oral morphine to oxycodone ratio has been generally accepted amongst treating clinicians and researchers. Oxycodone is frequently used in the chronic pain population. The sponsor has documented a recent 220-fold increase in single-entity prescriptions for oxycodone and a trend towards the prescribing of higher doses. As with all opiates used in this population, titration to effect commonly results in higher than standard doses due either to progression of pain and disease, or to the development of tolerance.

In their reassessment of the safety data, the sponsor included a comparative analysis of oxycodone versus Percodan® based on the findings in Study XIR0299, a revised and retabulated Integrated Summary of Safety based on TDD for the immediate release formulation, and a summary of safety data from the literature for doses greater than 60 mg.

Study XIR0299 Safety Data:

There were no deaths, serious adverse events, or discontinuations due to adverse events in this study. The most common adverse events in the oxycodone and Percodan® groups were lightheadedness (32%, 15%), nausea (32%, 15%), vomiting (28%, 19%), itching (16%, 19%), headache (16%, 8%), pallor (12%, 0), dizziness (9%, 15%), tiredness (9%, 4%), and feeling cold (9%, 8%).

Integrated Summary of Safety [ISS]:

The sponsor has pooled data from ten studies. Five of these studies were Phase 1 pharmacokinetic and bioavailability studies in healthy, opioid naïve volunteers. The

other five studies were Phase 2/3, two of which were open-label safety studies with one being an extension of the other. Only the data from the first of these two were presented by the sponsor in the ISS. Only the data from the immediate release formulations were included in this reanalysis. As documented in Dr. Blatt's Table 6, page 18 of his review, the incidences of deaths, serious adverse events, and adverse events resulting in discontinuation actually appeared to decrease in a dose dependent manner with the highest incidences in the less than 60 mg TDD group and lower incidences in the Treatment Period compared to the Stabilization Period.

There were a total of three deaths in the entire database. While two of those deaths do, based on the information available, appear to be related to progression of underlying disease, patient 15/1501 may have aspirated due to the sedative effect of the study drug.

Eight patients had serious adverse events, including the three deaths. Patient 15/1501 may well have aspirated due to the sedative effect of the oxycodone as noted above. In addition, patient 09/0905 may also have aspirated due to somnolence resulting in pneumonia and death. Patient 14/1405 apparently died of an overdose of drug possibly related to confusion or suicidal ideation caused by study drug exposure. However, each of these events is typical of high dose opiate use and the incidences of these types of events is not unusually high for this group of drugs.

A total of 61 patients were discontinued from studies due to adverse events. Based on review of Dr. Blatt's Table "Summary Table of Discontinuation" in the addendum to his review, the were no unexpected, clinically relevant adverse events or adverse events typically associated with opiate drugs occurring at an unusually increased incidence. The adverse events leading to discontinuation occurring with the greatest frequency (greater than 3%) were: vomiting (33%), nausea (25%), confusion (11%), pruritus (8%), dizziness (7%), and somnolence (7%). None of these events displayed a dose related effect.

A total of 538 patients were exposed to the immediate release formulation of Roxicodone, which includes the 5, 15 and 30 mg tablets. The sponsor's retabulation of the overall adverse events experienced in this patient pool grouped the subjects into which one of the following three dose ranges they fell into at the time the adverse event occurred: less than 60 mg/day; 60 to 120 mg/day; or, greater than 120 mg/day.

During the Stabilization Period of the study, patients in the highest dose range group had the highest incidences of adverse events in the following organ systems: body as a whole, digestive, respiratory, and skin and appendages. The following adverse events occurred with a dose related increase in incidence: nausea (13%, 24%, 30%); vomiting (7%, 16%, 16%); constipation (9%, 12%, 13%); dry mouth (3%, 3%, 7%); and insomnia (3%, 6%, 8%).

During the Treatment Period of the study, patients in the highest dose range group had the highest incidences of adverse events in the following organ systems: digestive, body

as a whole, and nervous. During this period, the incidence of nausea was lowest in the high dose group (8%, 12%, 2%). The incidence of vomiting was also lowest in the high dose group (10%, 7%, 4%); and the incidence of constipation was lowest in the mid-range dose group (8%, 2%, 7%).

There were no clinically relevant differences in the adverse event profile based on race, age or gender. There were no laboratory abnormalities or vital sign changes that were unexpected, related and of significant clinical relevance.

There are no pediatric data provided in this NDA.

Literature Review:

The sponsor's literature review of the safety of oxycodone provided only information from active controlled trials. Only one of these trials used the formulation that is the subject of this application. The information in these studies provided no useful data that could be analyzed for this review.

CHEMSITRY, MANUFACTURE AND CONTROLS

Dr. Maturu's primary review of CMC refers to a finding from one FDA laboratory on analysis of the drug product of a degradation product that exceeded the ICH guidelines for qualification. The peak was not seen on the sponsor's chromatographic data. Due to the fact that there was no acute or chronic preclinical testing required of this product in this 505(b)(2) application it could not be considered as qualified. On repeat testing, however, this degradation product could not be seen in the chromatographs from two independent laboratories (including the laboratory that originally described it). It was therefore attributed to a

NOMENCLATURE:

On review of the proprietary name Roxicodone, both the Office of Post-Marketing Drug Risk Assessment [OPDRA] and the Office of Generic Drugs [OGD] have found numerous instances of medication errors associated with the Roxi line of products, some resulting in fatalities.

. OPDRA also recommended a change in name for the Roxi product, which is the subject of this pending application. Review of the limited information about the known medication errors reported to the Agency indicated that the more serious events occurred due to errors in citing the correct dosage form, i.e., the prescriber writing

[/S/]

Cynthia G. McCormick, M.D.

8/31/00

August 31, 2000

Cc: Original NDA 21-011
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Blatt
Kim
Milstein

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care and Addiction Drug Products

MEMORANDUM

to: Division File, NDA # 21-011

from: Cynthia McCormick, MD /S/
Director,
Division of Anesthetics, Critical Care and Addiction Drug Products

subject: Roxicodone™ IR (Oxycodone Hydrochloride Tablets USP Immediate Release 15 mg, and 30 mg)

sponsor: Roxane Laboratories

date: September 16, 1999

This memorandum will summarize for the file the basis for the action to be taken on the NDA 21-011 for Roxicodone™ IR (Oxycodone Hydrochloride Tablets USP Immediate Release 15 and 30 mg) an opiate analgesic proposed for the treatment of moderate to severe pain in patients for whom oral opiates are indicated for more than a few days.

Background

Oxycodone is a semisynthetic pure μ-opioid agonist, which has been available in an immediate release formulation since the 1920's as an analgesic. It has undergone limited study through the intervening years as it was early on accepted to be intermediate in strength between morphine and codeine given orally. Currently oxycodone exists in the marketplace in many forms by virtue of DESI evaluation for the immediate release product, 5 mg. in combination with aspirin (Percodan), ANDA approval for oxydocodone with acetaminophen based on similarity to Percodan, and more recently NDA approval for pure oxycodone controlled release based on controlled studies. The currently available oxycodone IR 5-mg product that is being marketed as a single entity analgesic has no historical basis for approval.

This NDA #20-011 is intended to provide for an extension of the IR oxycodone line beginning as a 5-mg tablet to now include 15 and 30 mg. This NDA contains no efficacy data, but rather pharmacokinetics and limited safety supporting the higher doses. It presents a problem the root of which is the basis for the determination of efficacy of single entity oxycodone immediate release. The relevant regulatory history of oxycodone is reviewed below.

Oxycodone was first marketed in the United States in 1926.

The National Research Council/National Academy of Sciences Panel on Drugs for Relief of Pain, Panel on Drugs used in Rheumatic Diseases, and Panel on Neurologic Drugs all reviewed

the oxycodone products as part of the Drug Efficacy Study Implementation (DESI) process. A summary was published on November 18, 1971. The comments which accompanied this review and which are critical to this evaluation are·

> Oxycodone, aspirin and phenacetin are effective analgesics, even though this particular mixture (Percodan) may not be the best method of making use of these agents. Recent studies indicate that intramuscular oxycodone is approximately two-thirds to three-fourths as potent as morphine if consideration is given to both intensity and duration of effect. Oxycodone has a good oral-parenteral efficacy ratio compared with most narcotics. In recent experiments it proved about half as potent by mouth as by injection (considering both duration and intensity of effect)[1].

Discussion regarding the use of analgesic mixtures was touched on in a general sense as follows:

> There is increasing evidence, which has accumulated particularly within the past few years, that it is not always easy to predict the effects of adding one drug to another. Thus drugs may merely summate in their activities, antagonize each other, or produce true potentiation. Since adequate trials on the relative efficacy of single drugs and mixtures are usually unavailable, it is hard for the Panel [on Drugs for Relief of Pain] to be both fair and scientific in the evaluation of many of the mixtures which it has been asked to review.

In making its determination about the efficacy of Percodan, (containing oxycodone 5mg in an immediate release formulation) the Panel considered both clinical and nonclinical evidence of the efficacy of oxycodone. This included European data and experience with a single entity oxycodone product, which had been marketed for the treatment of moderate to severe pain as well as numerous relative analgesic potency studies performed in animals comparing codeine, oxycodone, and morphine.

The deliberations of this panel are summarized in the Percodan file and a right of reference has not been obtained by Roxane to reference these documents, however, it is clear that the agency has made the finding of safety and efficacy regarding immediate release oxycodone 5 mg.

The sequence of events that led to the approval of the first oxycodone product are as follows:

- DESI announcement was published in the FR on April 20, 1972 classifying Percodan tablets and Nucodan tablets as "**possibly effective** for moderate to moderately severe pain". This somewhat provisional finding was based solely upon the lack of justification for the inclusion of homatropine terephthalate in either formulation and of pentylenetetrazol in the second formulation.

- Endo subsequently submitted a supplement to NDA 7337 to reformulate only Percodan and change labeling as requested. The revised formulation eliminated homatropine terephthalate.

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[1] Documentation: Beaver AmerJ. Med Sci (250:577-604), 1965

This supplement was approved, resulting in the current formulation of Percodan on the market.

- A notice in the FR was published on December 9, 1972 stating that reformulations are effective for relief of moderate to moderately severe pain.

- No new evidence of effectiveness was submitted for the old formulations and so a Federal Register notice "Notice of Opportunity for a Hearing: Combination Drugs Containing Oxycodone with Homatropine or Pentylenetetrazol" on a proposal to withdraw approval of portions of the Endo Laboratories NDA-7337 for two products was published on December 10, 1973.

- Withdrawal of approval notice was published in the FR on April 23, 1975.

Efficacy

There are no data submitted in support of effectiveness of oxycodone 15 and 30 mg in this application. The sponsor has also not linked the proposed product to one for which the FDA has made the findings of safety and efficacy with relative bioavailability or bioequivalence studies. Such an approach would be considered acceptable. The case for the efficacy of 15 and 30 mg oxycodone immediate release has also not been effectively argued by the Sponsor in this application and must be done.

Of course, an equally worthy approach would be for the sponsor to submit, pursuant to 505(b)(1) of the Act, adequate and well-controlled studies supporting the efficacy of the immediate release single entity product in doses of 15 and 30 mg.

In review of these historical materials and the Agency's approach to similar products over the course of the ensuing 20 years, there is sufficient record that oxycodone 5-mg immediate release was considered to be effective as an analgesic at the time of and by the standards used in the DESI process. Since the combination policy was not effective at that time, the contribution of oxycodone to the overall effect of the analgesic mixture, as alluded to by the Panel, was not isolated, but was nevertheless characterized as predominant.

Safety—nonclinical

The sponsor has summarized the literature on the toxicology for oxycodone in this application. Much of the information provided can be considered general knowledge about opiate products and the relative potency data was considered at the time of the DESI review of Percodan. The applicant's compliance with the requirements under 21 CFR 314.92b for a waiver of preclinical safety studies under 314.50(d)(2) is not necessary for the agency to evaluate this application for preclinical safety given the more than 50 years of marketing experience and records of an adequate adverse event profile (see below). There are no specific data on carcinogenicity, mutagenicity, or reproductive toxicology, however.

The finding of safety has been made by the agency for identical, relative and similar products to Percodan. This finding may have been in part based upon the many years of use of this product. Nevertheless, the division is mindful of the fact that these findings did not include a careful evaluation of carcinogenicity and reproductive toxicology at that time. A benign profile cannot be assumed simply because of lack of association in the post-marketing experience. Therefore the sponsor will be expected to carry out carcinogenicity studies to support chronic dosing and the reproductive studies as well. However, given the prior finding of safety and the fact that oxycodone is currently on the market in multiple formulations these may be deferred to post marketing, phase IV commitments. The product labeling should in the meantime reflect their absence.

Safety–clinical

Since this NDA consisted mainly of biopharmaceutical studies, the duration of exposure was limited. Overall numbers of patients was also small (31 patients receiving 15 mg, and 38 patients receiving 30 mg). There were an additional 125 patients who received the 5-mg tablet, but in doses exceeding 5 mg/day. Total daily dosage in this NDA ranged from 60 mg (N=52); 60 to >120 mg/day (N=85) and 120 mg/day (N=54). This dosing paradigm implies that patients varied from opiate naive to tolerant and over one third were taking more than 30 mg q 6 hours. Adverse events were typical of opiate narcotics, with a dose response for GI side effects noted. There were no unexpected adverse events in any group.

An internal review of the adverse event reports submitted to FDA for all oxycodone products for the last 30 years was conducted and provided assurance of the safety of the drug product as also provided from the literature.

Biopharmaceutics

The bulk of this application consists of biopharmaceutical studies. These include a comparison of the 30-mg IR tablet with the 5 mg IR (marketed, unapproved) showing that the 30-mg tablet was bioequivalent to an equivalent dose of the 5-mg IR tablets. The to-be-marketed 15-mg formulation was also compared to the currently marketed 5-mg tablets and found to be bioequivalent. A dose proportionality study was performed at doses of 5 mg, 15 mg and 30 mg of IR oxycodone. It is of some interest that in this study pharmacodynamic measurements were obtained in an effort to determine of there is an efficacy dose response to the cold pressor test[2] after a single dose of medication. A nonlinear dose response was noted.

These results would be sufficient to approve the 15- and 30-mg tablets based on bioequivalence to the 5-mg tablets. The dilemma is, again, the paucity of findings of efficacy of oxycodone apart from an analgesic mixture, and the studies linking this product to an unapproved drug.

The sponsor will need to do further studies creating a "bridge" to an approved drug product containing oxycodone 5-mg in which the determination of efficacy was made. Percodan would be such an example, but a more recent example with specific data demonstrating the separate contribution of oxycodone 5-mg to efficacy would be preferable.

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[2] This is an experimental but validated screen for analgesic drug effect performed in the laboratory setting generally in healthy volunteers.

Chemistry and Manufacturing

The chemistry and manufacturing documentation, — stability data, QC methods and inspections of manufacturing sites are all acceptable for the 15 and 30 mg oxycodone IR formulation.

Regulatory

This drug was submitted as a 505(b)(1) application rather than as a 505(b)(2). Sponsor has been (by teleconference call) requested to correct this error, and refile the 356h as a 505(b)(2), identify those portions of the application rely on literature, the agency's prior findings of efficacy, and studies for which Roxane does not have right of reference. The requisite relative bioavailability studies comparing this product to the "listed drug" oxycodone IR are, however, in question since the existing marketed product is neither a grandfathered nor a DESI drug. The final approval will likely be contingent on the ability of the sponsor to demonstrate the efficacy of oxycodone either as the 5-mg tablet or to make the link with relative bioavailability studies to Percodan (oxycodone and ASA) the listed drug with a DESI approval or any other marketed combination product (such as oxycodone/ibuprofen or acetaminophen) for which the finding of safety and efficacy was made for oxycodone IR 5 mg.

Of course, the sponsor may also provide clinical trials for any of the IR dosage forms (5 mg, 15 mg and 30 mg). This would be a preferable alternative.

Data Integrity

There were no clinical inspections and review of the data revealed no issues to suggest a scientific misconduct or fraudulent data.

Summary of Deficiencies

Efficacy

A prior finding of efficacy of the 5-mg oxycodone tablet, immediate release alone is not well documented. In the course of the DESI evaluation of Percodan the NAS Panels made the assumption that oxycodone was the principal active ingredient in the combination. These deliberations were recommendations to the FDA, which then approved the combination product Percodan. If subsequent combination products were approved in the era of combination drug policy, oxycodone IR 5 mg might have been evaluated as a single entity. This was not the case. Percodan, then remains as the standard listed drug providing the basis of efficacy against which Roxane could bolster its application as a 505b2 application.

The sponsor will be expected to (1) provide the relative bioavailability studies against which the Agency can extrapolate its prior findings and (2) provide an adequate rationale for the extension of the dose to 15 and 30 mg without having provided studies demonstrating efficacy at the higher doses. Such a rationale could invoke relative potency data comparing oxycodone doses of 15 and 30 mg to morphine or codeine, data on tolerance development that can be expected during a period of treatment necessitating titration of doses upward to as high as 30 mg, or

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pharmacokinetic/pharmacodynamic data obtained from other formulations either controlled release or immediate release products that have supported efficacy at the higher dose.

Safety
Clinical safety in the higher doses has not been adequately established with a database of approximately 30 patients in either group and no chronic exposure data are available.

In order for this NDA to be approved, the sponsor will have to provide sufficient safety data at the proposed doses for marketing.

Regulatory
Clearly as this application has implicitly relied upon the finding of efficacy of oxycodone and has provided no data of its own, a 505b2 application should have been filed. The reference-listed drug should be identified, as well as the appropriate patent certifications and data on relative bioavailability to this drug provided.

Phase 4 Commitments

The sponsor will be asked to provide studies in the following areas in the post-marketing phase:

- Carcinogenicity studies to support chronic dosing
- [redacted]

Action

This application is not presently in a condition to be approved, however with the correction of the above deficiencies, there should be no impediments to approval. An approvable letter should be sent to the sponsor outlining the deficiencies and those steps needed to correct them.

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will briefly review the evidence of effectiveness and safety summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

The only studies submitted in support of efficacy were an open-label, nonrandomized safety study with some pain measurements defined as secondary outcome measures, XIR0596, and the open-label extension study to XIR0596, XIR0696. Although Dr. Li does discuss these studies in the efficacy section of his NDA review, they do not provide any scientifically sound information regarding the effectiveness of the oxycodone 15 and 30 mg tablets. Dr. Li also reviewed Studies CBI-961/962, CBI-1252 and CBI-963 as supportive of efficacy. These three studies were the subject of the sponsor's NDA 20-932 for Roxicodone SR, 10 mg and 30 mg tablets. They compared these slow release formulations to equivalent doses of an immediate release formulation marketed as 5 mg tablets. The 5 mg immediate release formulation has been sold in the U.S. since the 1930's but has never received any formal type of approval from the Agency. The 15mg and 30 mg immediate release formulations, which are the subject of this application, were not used in the three CBI studies.

Thus, no evidence of the effectiveness of the oxycodone hydrochloride 15 mg and 30 mg immediate release tablets has been submitted in this application.

SAFETY:

The safety database reviewed by Dr. Li is based on ten completed studies. Five of those studies were Phase I pharmacokinetic and bioavailability studies (315-05, 315-07, XIR0396, XIR0296 and XIR0196) that were conducted in healthy volunteers. The other five studies include the open-label safety studies XIR0596 and XIR0696, as well as the three CBI studies noted above. Dr. Li included those studies in the review database because they included patients treated with the 5 mg immediate release [IR] formulation. However, I will attempt to separate out the available safety data based on whether their was exposure to the 15 and 30 mg IR tablets, the 5 mg IR tablet, or a combination of products.

Study XIR0696 is an extension of Study XIR0596 and the patients are the same in both studies. Thus, Study XIR0696 patients were not included as additional patients in the pooled ISS analysis. The sponsor grouped all patients who received even one dose of the 30 mg tablet into a "30 mg group"; these patients may have received 15 mg tablets. Patients who only received 15 mg tablets during the entire study period were grouped into a "15 mg group."

A total of 70 subjects were exposed to oxycodone in the pharmacokinetic studies, 25 to 15 mg tablets and 45 to 30 mg tablets. A total of 104 patients were exposed to oxycodone in the clinical studies, 56 to 15 mg tablets and 48 to 30 mg tablets. The sponsor did not combine all patients or subjects for analysis of average total daily dose exposure. Based on the analyses that the sponsor did document, the mean total daily dose during the Stabilization Period of Study XIR0596 for the 56 patients in the "15 mg group" was 79 mg. The mean total daily dose during the Stabilization Period of Study XIR0596 for the 48 patients in the "30 mg group" was 157 mg. The mean total daily dose during the Treatment Period of Study XIR0596 for the 31 patients in the "15 mg group" was 85 mg. The mean total daily dose during the Stabilization Period of Study XIR0596 for the 35 patients with dosing information (out of a total of 38 patients) in the "30 mg group" was 151 mg.

The following three tables, copied from Dr. Li's Tables 17, 18 and 19, pages 43, 44 and 45 of his review, also provide some information about exposure to oxycodone IR 15 and 30 mg during the clinical drug development period.

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Table 1.

Study: XIR0596 Duration of Exposure by Average Total Daily Dose for Each Formulation - *Stabilization Period*				
	Number (%) of Patients Exposed			
	Average Total Daily Dose (mg/day) of Oxycodone IR[a]			
Therapy Duration (days)	**<60 n (%)**	**60-120 n (%)**	**>120 n (%)**	**Total n (%)**
15 mg (N=56)				
≤ 7	4	13	1	18 (32%)
>7-14	7	20	8	35 (63%)
>14	2	1	0	3 (5%)
Overall	**13 (23%)**	**34 (61%)**	**9 (16%)**	**56 (100%)**
30 mg (N=48)				
≤ 7	0	6	5	11 (23%)
>7-14	0	12	20	32 (67%)
>14	0	2	3	5 (10%)
Overall	**0 (0%)**	**20 (42%)**	**28 (58%)**	**48 (100%)**
Total (N=104)	**13 (13%)**	**54 (52%)**	**37 (35%)**	**104 (100%)**

[a] Each patient's average TDD (including rescue medication) was calculated based on the number of days of dosing

Denominator used to calculate the percent is 56 patients for the 15 mg group, and 48 patients for the 30 mg group

Total indicates the total number of patients exposed to each therapy duration for each formulation group

Overall indicates the overall number of patients averaging a TDD in each TDD category for each formulation group

Study: XIR0596

Source: the sponsor's Table 2.1

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Table 2.

Study: XIR0596 Duration of Exposure by Average Total Daily Dose for Each Formulation - *Treatment Period*				
	Number (%) of Patients Exposed			
	Average Total Daily Dose (mg/day) of Oxycodone IR[a]			
Therapy Duration (days)	<60 n (%)	60-120 n (%)	>120 n (%)	Total n (%)
15 mg (N=31)				
≤ 7	3	1	1	5 (16%)
>7-14	7	14	5	26 (84%)
>14	0	0	0	0 (0%)
Overall	10 (%)	15 (48%)	6 (19%)	31 (100%)
30 mg (N=38)				
≤ 7	0	3	4	7 (18%)
>7-14	0	8	19	27 (71%)
>14	1	0	0	1 (3%)
Overall	1 (3%)	11 (29%)	23 (61%)	35 (92%)[b]
Total (N=69)	11 (16%)	26 (38%)	29 (42%)	66 (96%)[b]

[a] Each patient's average TDD (including rescue medication) was calculated based on the number of days of dosing

[b] Three patients were missing dosing information; therefore, the total for the 30-mg group is 35 instead of 38 and is 66 instead of 69 for the overall total.

Denominator used to calculate the percent is 31 patients for the 15 mg group, and 38 patients for the 30 mg group

Total indicates the total number of patients exposed to each therapy duration for each formulation group

Overall indicates the overall number of patients averaging a TDD in each TDD category for each formulation group

Study: XIR0596

Source: The sponsor's Table 2.2.

Table 3.

Long Term Exposure - Extension Study XIR0696			
	Number (%) of Patients Exposed		
	Oxycodone IR Formulation		
Duration (days)[a]	15 mg (N= 19)	30 mg (N= 31)	Overall (N= 50)
1-14	2 (11%)	1 (3%)	3 (6%)
>14-28	6 (32%)	4 (13%)	10 (20%)
>28 (Max = 39 days)	11 (58%)	26 (84%)	37 (74%)
Total	19 (100%)	31 (100%)	50 (100%)

[a] Does not include patients' prior exposure to oxycodone during the XIR0596 study

Denominator used to calculate the percent is 19 patients for the 15 mg group, and 31 patients for the 30 mg group

Total indicates the total number of patients exposed to each formulation group

Overall indicates the overall number of patients in each duration of exposure category

Study included: XIR0696

Source: Sponsor's Table 6.1 of individual study report

Deaths:

Three deaths were reported from the clinical studies. One 80 year old male patient in the 30 mg group died of heart failure believed to be due to progression of lung cancer. His average total daily dose of oxycodone was 52 mg. A 54 year old male patient in the 15 mg group with metastatic gastrointestinal carcinoma died of aspiration pneumonia while in a hospice. His average total daily dose of oxycodone was 60 mg. The investigator believed that the death was not related to study drug. A 46 year old woman with metastatic breast cancer whose death was believed to be due to progression of disease had been treated with a total average daily dose of 60 mg of oxycodone, using the 5 mg tablets.

Discontinuations:

Three out of 70 subjects in the pharmacokinetic studies discontinued due to adverse events. All 3 of these subjects were in the "30 mg group", n = 45. The adverse events for which these 3 subjects discontinued were: intercurrent illness (flu symptoms) in one subject, sinus and urinary tract infections in a second subject, and upper respiratory infection in the last subject.

Twenty-six out of 104 patients (21/56 in the "15 mg group" and 5/48 in the "30 mg group") were discontinued due to adverse events during the Stabilization Period of XIR0596. During the Treatment Period, 2/31 patients in the "15 mg group" and 1/38 patients in the "30 mg group" were discontinued due to adverse events. In the Extension Study XIR0696, 2/19 patients in the "15 mg group" and 2/13 patients in the "30 mg group" were discontinued due to adverse events.

The most common adverse events resulting in discontinuation during the Stabilization Period of XIR0596 were nausea and vomiting. Also reported were: abnormal vision, confusion and hypertension, each occurring in one patient, and nervousness, pruritus and somnolence, each occurring in two patients. These adverse events appeared to occur more frequently in patient's in the "15 mg group." Dr. Li's Table 7, page 24 of his review summarizes the relevant data regarding these patients. That table also shows a 27th patient with "pain." Dr. Li reports that the patient was included in the table in error.

During the Treatment Period of XIR0596, one patient in the "30 mg group" discontinued due to cardiorespiratory/heart failure. Two patients in the "15 mg group" discontinued; one due to drowsiness/somnolence and one due to disorientation/confusion. In the Extension Study, the four patients discontinued due to cerebrovascular accident, gastrointestinal carcinoma/aspiration pneumonia (same patient as noted under Deaths above), pneumonia and rash.

Serious Adverse Events:

A total of 5 patients experience serious adverse events during the clinical studies. The following table, copied from Dr. Li's review, page 41, summarizes the important data regarding these five patients.

Table 4.

Serious Adverse Events Reported During the Clinical Studies (XIR0596/0696)							
Study No. Period.	**Site No. /Patient No.**	**Age (yr.)**	**Gender**	**IR Tablet Group**	**Average TDD (mg/day)**	**COSTART Term and SAE Classification**	**Relation to Study Drug**
XIR0596 Treatment	04/0403	80	Male	30 mg	52 mg/day	Heart failure resulting in death	Unlikely
XIR0596 Treatment	14/1405	41	Female	15 mg	55 mg/day	Confusion and personality disorder, the signs and symptoms of an overdose	Related
XIR0696 Extension	09/0905	57	Female	15 mg	60 mg/day	Pneumonia resulting in prolonged hospitalization	Not related
XIR0696 Extension	15/1501	54	Male	15 mg	60 mg/day	Aspiration pneumonia resulting in prolonged hospitalization and death	Not related
XIR0696 Extension	04/0402	64	Male	30 mg	180 mg	Cerebrovascular accident (stroke) resulting in prolonged hospitalization	Not related

Note that patients 1405 and 1501 were also included in Dr. Li's discussion of deaths during the clinical trials.

Five patients treated with the 5 mg tablets experienced serious adverse events in the clinical studies, including the patient (# 0002) noted in Dr. Li's discussion of deaths during the clinical trials (See Dr. Li's Table 16). No subjects experienced serious adverse events during the pharmacokinetic studies.

Other Adverse Events:

Dr. Li's Table 29 on page 56 of his review displays the adverse events occurring in the pharmacokinetic studies with an incidence of ≥3%. In order to focus on the events occurring specifically in subjects exposed to the 15 mg and 30 mg tablets, I have copied the data for those subjects in the table below:

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Table 5.

Incidence of Adverse Events (≥3%) by Body System Human Pharmacokinetic and Bioavailability Studies		
Number (%) of Subjects		
	Oxycodone IR Formulations	
Body System COSTART Term	15 mg (N=25)	30 mg (N=45)
Body as a Whole		
Fatigue	7 (28%)	3 (7%)
Asthenia	1 (4%)	11 (24%)
Headache	0 (0%)	14 (31%)
Temperature Changes	0 (0%)	2 (4%)
Cardiovascular System		
Vasodilation	1 (4%)	6 (13%)
Digestive System		
Dyspepsia	1 (4%)	3 (7%)
Hiccup	5 (20%)	4 (9%)
Dry Mouth	1 (4%)	5 (11%)
Vomiting	9 (36%)	9 (20%)
Nausea	13 (52%)	14 (31%)
Nervous System[a]		
Dizziness	15 (60%)	23 (51%)
Somnolence	3 (12%)	14 (31%)
Euphoria	2 (8%)	0 (0%)
Paraesthesia	0 (0%)	0 (0%)
Tremor	1 (4%)	4 (9%)
Nervousness	0 (0%)	1 (2%)
Confusion	0 (0%)	0 (0%)
Skin and Appendages		
Pruritus	8 (32%)	18 (40%)
Sweat	0 (0%)	6 (13%)
Increased Sweat	0 (0%)	4 (9%)

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Of note are the high incidence of fatigue, asthenia, headache, hiccup, vomiting, nausea, dizziness, somnolence and pruritus.

Dr. Li's Table 24 on page 49 of his review (copied below) displays the adverse events occurring in Study 0596. Of interest are the high incidence of headache, constipation, nausea, vomiting, dizziness, somnolence and pruritus during the Stabilization Period, which become less frequent during the Treatment Period:

Table 6.

Incidence of Adverse Events ≥3% by Body System – Study XIR0596				
	Number (%) of Patients			
	Stabilization Period	Stabilization Period	Treatment Period	Treatment Period
Body System COSTART Term[a]	15 mg (N=56)	30 mg (N=48)	15 mg (N=31)	30 mg (N=38)
Mean TDD	79 mg	157 mg	85 mg	151 mg
Median TDD	64 mg	130 mg	73 mg	148 mg
Body as a Whole	15 (27%)	12 (25%)	11 (36%)	4 (11%)
Asthenia	1 (2%)	0 (0%)	1 (3%)	1 (3%)
Headache	9 (16%)	6 (13%)	2 (7%)	2 (5%)
Pain	2 (4%)	4 (8%)	2 (7%)	1 (3%)
Cardiovascular System	1 (2%)	2 (4%)	0 (0%)	1 (3%)
Digestive System	29 (52%)	24 (50%)	10 (32%)	9 (24%)
Constipation	9 (16%)	12 (25%)	4 (13%)	6 (16%)
Nausea	18 (32%)	14 (29%)	5 (16%)	2 (5%)
Vomiting	14 (25%)	9 (19%)	3 (10%)	1 (3%)
Nausea and Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hemic and Lymphatic System	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Metabolic and Nutritional System	1 (2%)	1 (2%)	0 (0%)	1 (3%)
Musculoskeletal System	2 (4%)	1 (2%)	0 (0%)	0 (0%)
Nervous System	22 (39%)	15 (31%)	5 (16%)	8 (21%)
Dizziness	11 (20%)	4 (8%)	2 (7%)	1 (3%)
Dry Mouth	0 (0%)	3 (6%)	0 (0%)	1 (3%)
Insomnia	3 (5%)	3 (6%)	2 (7%)	2 (5%)
Somnolence	7 (13%)	4 (8%)	1 (3%)	1 (3%)
Respiratory System	3 (5%)	8 (17%)	4 (13%)	2 (5%)
Skin and Appendages	11 (20%)	11 (23%)	4 (13%)	3 (8%)
Pruritus	7 (13%)	9 (19%)	2 (7%)	2 (5%)
Sweating	4 (7%)	2 (4%)	1 (3%)	0 (0%)
Special Senses	2 (4%)	0 (0%)	1 (3%)	0 (0%)
Urogenital System	2 (4%)	1 (2%)	0 (0%)	0 (0%)

[a] The adverse event COSTART term is included if the overall incidence is ≥3%

Study: XIR0596

Data Source: sponsor's Tables 3.2.1 and 4.2.1

Review of the sponsor's Table 6.6.1, Volume 50, pages 159-161, which displays the complete list of adverse events for XTR0596, does not reveal adverse events of significant frequency and concern, other than those that would be expected with an opioid drug product.

Dr. Li's Table 25 on page 51 of his review (copied below) displays the adverse events occurring in the four week extension Study 0696:

Incidence of Adverse Events by Body System and COSTART Term (An AE ≥ 10%)
Study XIR0696

Body System COSTART Term[a]	Number (%) of Patients		
	15-mg Group (N=19)	30-mg Group (N=31)	Overall (N=50)
Body as a Whole	**7 (37%)**	**4 (13%)**	**11 (22%)**
Headache	2 (11%)	2 (7%)	4 (8%)
Pain	2 (11%)	1 (3%)	3 (6%)
Cardiovascular System	**0 (0%)**	**1 (3%)**	**1 (2%)**
Digestive System	**8 (42%)**	**9 (29%)**	**17 (34%)**
Constipation	2 (11%)	7 (23%)	9 (18%)
Nausea	3 (16%)	1 (3%)	4 (8%)
Hemic and Lymphatic System	**0 (0%)**	**0 (0%)**	**0 (0%)**
Metabolic and Nutritional System	**0 (0%)**	**1 (3%)**	**1 (2%)**
Nervous System	**4 (21%)**	**2 (7%)**	**6 (12%)**
Insomnia	2 (11%)	1 (3%)	3 (6%)
Respiratory System	**4 (21%)**	**2 (7%)**	**6 (12%)**
Skin and Appendages	**1 (5%)**	**6 (19%)**	**7 (14%)**
Special Senses	**0 (0%)**	**0 (0%)**	**0 (0%)**
Urogenital System	**3 (16%)**	**0 (0%)**	**3 (6%)**

[a] The individual adverse event COSTART term is included if the incidence is ≥10% for any study
Study Presented: XIR0696
Data Source: The sponsor's Table 4.6.0, 6.5.2, and 6.5.3

Review of the sponsor's Table 6.5.3, Volume 54, pages 95-96, which displays the complete list of adverse events for XIR0696, does not reveal adverse events of significant frequency and concern, other than those that would be expected with an opioid drug product.

When pooled data for adverse events (occurring with a frequency of ≥3%) in patients exposed to the 5 mg IR tablet (see Dr. Li's Tables 27 and 28, pages 53 and 54 of his review) are compared to adverse events occurring in patients exposed to the higher dose preparations, there is no indication that the 5 mg tablet has a significantly different adverse event profile. Of note, however, many adverse events appeared to occur with a consistently higher incidence in the "15 mg group" compared to the "30 mg group" or the group exposed only to the 5 mg tablets. Both Dr. Li and the sponsor explained this finding as likely being due to the small sample size and the number of opioid-naïve

patients enrolled in this group. Dr. Ma, in his Statistical Review and Evaluation, concluded that patients with a lower Total Daily Dose were more likely to report adverse events in the Cardiovascular, Nervous and Respiratory systems than those patients with a higher Total Daily Dose; and, there was no actual increased adverse event incidence in patients treated with a higher total daily dose of oxycodone. He hypothesizes that the higher adverse event incidence in the "15 mg group" may have been due to a combination of there being more opiate naïve patients in this group, other differences in patient selection criteria, differences in adverse event reporting procedures, and differences in study management.

Laboratory Values:

There were no clinically significant laboratory abnormalities attributable to the study drug.

Vital Signs:

There were no clinically significant and unexpected changes in vital signs attributable to the study drug.

COMMENTS:

The sponsor has provided no evidence of efficacy for their oxycodone IR 15 mg and 30 mg tablets. While it is true that similar products have been available for many years and patients have found relief from their pain when treated with these products, the extent of placebo effect, accuracy of dosing recommendations, and proper characterization of the clinical response over time have never been established for those products. In addition, an appropriate linkage between those products and the new formulations is not supported by this application.

While there is a wealth of anecdotal evidence supporting the likely effectiveness of these new formulations, more information is necessary and essential to providing appropriate labeling for their use and documenting accurately the value of these products.

In addition, the safety database, especially for high dose and long-term exposure to these products is inadequate to support approval at this time. The overall safety profile, although as expected from an opioid drug product, is limited by the small numbers of patients exposed. Serious, drug specific adverse events do occur within the opiate drug class and, in spite of the long history of use, we have no prospective data for oxycodone documenting its safety profile in an accurate manner.

RECOMMENDATIONS:

1. The sponsor must provide additional evidence of efficacy for the oxycodone IR 15 mg and 30 mg tablets. This evidence could be in the form of new clinical efficacy trial data or data which is based on other oxycodone IR products for which clinical efficacy has been established.

2. The sponsor needs to increase the patient safety data base, especially for higher doses and longer-term treatment.

[/S/]

Bob A. Rappaport, M.D.

10/1999

September 10, 1999

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NDA 21-011 Addendum

FINANCIAL DISCLOSURE

On February 10, 2000, the sponsor submitted Certification: Financial Interests and Arrangements of Clinical Investigators form OMB NO. 0910-0396 and a Roxane Laboratories Investigator's Financial Disclosure Form. These forms certify that the sponsor has not entered into a financial arrangement with the investigator that is dependent on the outcome of the study. Further, that the investigator has not disclosed any proprietary interest in the product or equity in the sponsor's company. These statements appear to satisfy the financial disclosure requirements.

[/S/]

8-31-00

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CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 4/5/00	DUE DATE: 5/8/00	OPDRA CONSULT #: 00-0117

TO:

Cynthia McCormick, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH:

Judit Milstein
Project Manager
HFD-170

PRODUCT NAME:	MANUFACTURER: Roxane
Roxicodone (Oxycodone HCl Tablets, USP) 15 mg and 30 mg NDA #: 21-011	

SAFETY EVALUATOR: Peter Tam, RPh.

OPDRA RECOMMENDATION:

OPDRA does not recommend use of the proprietary name, Roxicodone.

[/S/]

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

[/S/] 7-17-00

Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

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Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

Proprietary Name Review

DATE OF REVIEW: 5/11/00

NDA#: 21-011

NAME OF DRUG: Roxicodone
(Oxycodone HCl Tablets, USP) 15 mg and 30 mg

NDA HOLDER: Roxane

I. INTRODUCTION:

This OPDRA consult is in response to a request received on April 5, 2000, from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) to review the proposed proprietary name Roxicodone. OPDRA conducted a post-marketing and pre-marketing review on the confusion with the root name "Rox" utilized for the analgesic products manufactured by Roxane.

PRODUCT INFORMATION

Roxicodone (Oxycodone HCl Tablets, USP) is an opioid analgesic. It is indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate. Each Roxicodone tablet contains 15 mg or 30 mg of oxycodone HCl, in a formulation that provides for immediate release of the medication. The analgesic ingredient, oxycodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those morphine; the most prominent of these involves the central nervous system and organs composed of smooth muscle.

About 60% to 80% of an oral dose of oxycodone reaches the systemic circulation in comparison to a parenteral dose. This high oral bioavailability (compared to other opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone. Oxycodone HCl is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. It is excreted primarily via the kidney.

Roxicodone should be individually dosed and adjusted according to severity of pain, patient response and patient size. Patients who have not been receiving analgesics should be started on Roxicodone in a dosing range of 5 to 15 mg every 4-6 hours as needed for pain.

Roxicodone will be available in 15 mg green scored and 30 mg blue scored tablets in bottles of 100 tablets and in unit dose cards containing 25 tablets per card.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product references texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Roxicodone to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (both inpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to stimulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

The panel discussion was conducted to gather professional opinions on the safety of the proprietary name Roxicodone. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communication (DDMAC). Roxicet, Roxanol, Roxilox and Roxiprin were identified as having the most potential for confusion with Roxicodone. All four proprietary names were derived from the root name, "Rox". These four products would be prescribed in the same clinical setting (both inpatient and outpatient), and have overlapping dosing intervals. Hence the potential for medication errors due to name confusion among these products is high (see below).

Product Name	Dosage form (s), Generic name	Usual Dose	Observation
Roxicodone	Tablets, 15 mg and 30 mg, oxycodone	5-15 mg q4-6 hrs	
Roxicet	Tablets, oxycodone/acetaminophen, 5/325 mg and 5/500 mg	One to two tablets q4-6 hrs	*S/A
Roxanol	Conc. soln, morphine 20mg/mL	Individualize, 0.5-1ml q6h	S/A
Roxilox	Capsules, oxycodone/acetaminophen, 5/500mg	One to two capsules q4-6hrs	S/A
Roxiprin	Tablets, oxycodone/ HCl,Terephthalate/Aspirin4 .5mg/0.38mg/ 325mg	One to two tablets q4-6 hrs	S/A

* S/A = sound alike[1]

[1] MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.